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EXAMINER
PORTNER, VIRGINIA ALLEN

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/545,199	LOWERY ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *19 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *7-24 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *7-24 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 32-33 have been canceled.

Independent claim 7, and dependent claims 12, 14, and 19 have been amended.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections Withdrawn

2. Claims 32-33 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the introduction of mutations into specific open reading frames, specifically the elected SEQ ID NO 3, for the production of an immunogenic recombinant bacteria, does not reasonably provide enablement for formulation of vaccines for any gram negative bacteria, with any mutation in SEQ ID NO 3, or a species homolog of SEQ ID NO 3, for the induction of a protective immune response, the full genus of which has not been enabled as vaccine compositions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims; has been obviated through cancellation of these claims.

3. Claims 8-12, 14-18, 21-24 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for not providing antecedent basis for recited claim limitations and further limiting the prior claim has been obviated by amendment.

Rejections Maintained

4. Claims 7-24, and 31 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons of record in paper number 23, dated June 11, 2003, and arguments in response to Applicant's Remarks, set forth below.

5. Claims 7-24 and 31, as previously applied to claims 8-24 and 31-33 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reciting the phrases "a gene" and species "homolog", for reasons of record in paper number 23.

6. Claims 7-24 and 31, as previously applied to claims 8-24, 31-33 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reciting mutations in homolog genes and gene products not clearly set forth in the claims, for reasons of record in paper number 23.

Response to Arguments

7. The rejection of claims 7-24, and 31 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, is traversed on the grounds that:

a. Applicant asserts that the instant Specification enables and describes mutations in polynucleotide sequences that encode the gamma subunit of ATPase of more than just two species of Pasteurellaceae;
b. Asserts that "one of skill in the art could make and use the invention of the pending claims without undue experimentation; and
c. Concludes that "there is no reason to limit the claims to the exemplary embodiments in the specification."

8. It is the position of the examiner that the rejection made of record was directed to written description and possession of the claimed invention at the time of filing the instant Specification. Arguments directed to only enablement (following guidance to make and use), does not address the issue of possession under the written description requirement under 35 USC 112, first paragraph.

What is now claimed is not limited to mutations within the open reading frame that encode "the gamma subunit of ATPase" set forth in SEQ ID NO 3, but is directed to mutant genes that comprise the coding sequences for gamma subunits of ATPase from any gram negative bacteria (see definition of the invention for homologs at Specification page 5, paragraph 2), to include functional homologs that have a similar activity, not requiring the same activity, which reads on other ATPase subunits (see instant Specification, page 47, Example 10, that teaches atpH as a homolog; also see page 16, paragraph 1, last three lines) , as well as mutations

in regulatory regions that modulate transcriptions of the virulence gene (see instant specification page 10, paragraph 2) and is therefore not limited to mutations within the coding sequence for the gamma subunit of ATPase of SEQ ID NO 3, or open reading frames that encode gamma subunits of ATPase.

In support for the examiner's positions that possession of the instant claimed genus of mutant genes contained within an attenuated bacteria, not having been so described to show possession at the time of filing, several references will be sited to show that gene placement in different strains and species of Pasteurellaceae differ from the strains and species exemplified in the instant specification.

9. Kroll et al (Oct. 1998) teaches Haemophilus (member of the Family of Pasteurellaceae) undergoes natural genetic exchange with Neisseria, to include intergeneric transfer of chromosomal genes providing evidence of horizontal transfer of genetic material between different Families of bacteria. Kroll et al provide evidence for chromosomal mosaicism between pathogenic bacteria, thus defining differences in gene location and operons within the bacterial chromosomes.

10. Oswald et al (July 1999) show physical maps of different Actinobacillus pleuropneumoniae serotype strains, which provide evidence for very distinct differences in chromosomal arrangement based upon differences in the sizes of macrorestriction fragments produces in the genomes of the exemplified strains. Different locations form genes would evidence different regulatory sequences and operon construction based upon the polynucleotide sequences with which they are associated (different size fragment locations for virulence genes, see Oswald et al, page 4163, col. 2, paragraph 3, middle of paragraph; Figure 2 and Table3).

Oswald et al concluded that the strains evaluated showed a high degree of homogeneity and stability within Actinobacillus pleuropneumoniae, but also concluded that H.influenzae sequences (a member of Pasteurellaceae) though useful for PCR and Southern blotting, do not provide or "allow a prediction of the relative locations of the corresponding A.pleuropneumoniae genes (see page 4168, col. 1, last paragraph and col. 2, first and second paragraphs)".

Absent specific guidance for the location of genes, the mutation of H.influenzae chromosomal locations would not correspond to locations in A.pleuropneumoniae. Genetic variability precludes exact site directed mutations in specific genes among members of a Family of bacteria, based upon the existence of variable locations for corresponding species homolog open reading frames.

Chevallier et al (1998) provide additional insights into Actinobacillus pleuropneumoniae genome size and polymorphism. Chevallier et al analyzed macrorestriction patterns to find the existence of a high degree of genetic polymorphism among different serotypes of the same species of Actinobacillus. While the overall size of the genome of Actinobacillus pleuropneumoniae was about 2.3 to 2.4 Mb, the chromosomal structure, thus the location of genes was heterogeneous; not the same location. Chevallier et al provide evidence that possession of a single mutant strain of Actinobacillus pleuropneumoniae with specific mutations in, say Applicant's SEQ ID NO 3, would not provide, evidence of possession of additional mutant strains within the Family of Pasterurellaceae that would differ based upon chromosomal /gene polymorphism.

Valcarcel et al (Feb. 1997) found upon genomic analysis 19 strains of Actinobacillus actinomycetemcomitans, found 13 different genetic profiles, and evidence of a high degree of

polymorphism within the single bacterial chromosome of each strain. Additionally, Valcarcel et al found the presence of large plasmids carrying up to 20% of the total genome's genetic material. Slots et al (1993) analyzed 73 strains of Actinobacillus actinomycetemcomitans and found 30 DNA profiles among the analyzed strains. Clearly. Valcarcel et al and Slots et al provide evidence for variability within the genomes of members of the Family of Pasteurellaceae, and possession of specific mutant attenuated strains of Pasteurella multocida and Actinobacillus pleuropneumoniae does not show possession of attenuated strains of additional members of the Family of Pasteurellaceae which evidence a high degree of polymorphism, and carry up to 20% of the total genomes genetic material on large plasmids (Valcarcel et al) and evidence distinct genetic regions in one of 30 different DNA profiles (Slots et al, abstract).

Hobbs et al (1996, abstract) analyzed Haemphilus ducreyi and compared the genome with that of Haemphilus influenzae, both members of the family of Pasteurellaceae. Hobbs et al found six rrn operons (genes in bacteria are contained in operons) in the compared Haemphilus species, and along with two distinct restriction patterns, thus providing evidence of different gene/open reading frame placement within the genomes of these bacteria. Butler et al (1990, abstract), Blackall et al (1991, abstract), and Bernstein et al (1989, abstract) all teach Haemophilus is known to be genetically heterogeneous.

The cited references provide evidence for differences in gene order, regulatory sequence locations, and operon placement within the chromosomes of members of Family of Pasteurellaceae. The disclosure two specific species within instant Specification does not provide original descriptive support for the instantly claimed genus of mutant strains of Pasteurellaceae bacteria; the Specification does not provide a representative number of species

of the claimed genus of mutant strains within a highly variable genus in light of the cited references which provide evidence that the Family of Pasteurellaceae bacteria represents a group of bacteria with distinctly different gene sequences, operon locations, chromosomal gene locations, and over all genetic organization.

11. Applicant asserts that the claims "are not directed to novel nucleic acids, which arguably would require a more detailed description of the structure".

12. It is the position of the examiner that what is now claimed are mutant strains of bacteria that comprise a mutant gene, which is a nucleic acid, and the mutant nucleic acid sequence is what defines the patentable novelty of the instantly claimed invention. The prior art teaches attenuated strains of Pasteurella (Fuller et al US Pat. 6,410,021 rib gene mutant; Briggs et al, AroA mutant strains(US Pat. 5,587.305) therefore novelty is defined by the mutant gene regulatory sequence associated with the nucleic acid sequence that encodes atpG or the mutant nucleic acid within an atpG gene or homolog (bacterial operon) having been introduced into Pasteurella multocida or Actinobacillus pleuropneumonia. Clearly the nucleic acid that encodes atpG and homologs thereof are critical to the claimed invention, and a detailed description of the gene structure is essential to showing possession of the claimed invention.

13. Applicant traverses the lack of written description rejection under 35 USC 112, first paragraph over the genus of claimed mutant strains based upon the guidance and teaching provided in Examples 1, 2 and 5.

14. The examiner upon reconsideration of the guidance and teaching of Example 1, found the example to teach the construction of a library of randomly generated tagged transposon

P.multocida mutants. Example does not provide evidence of possession of the instantly claimed genus of mutant strains of Pasteurellaceae bacteria with a mutation in the atpG gene locus.

Upon reconsideration of the guidance and teaching of Example 2, the examiner found the Specification to teach a murine screen for attenuated strains of Pasteurella multocida. The screen is taught for use with any type of mutant strain (see Specification page 36, paragraph 2, lines 23-29), this does not show **possession** of the instantly claimed genetically highly variable genus of strains of Pasteurellaceae with specified mutations in the atpG gene or gene homolog, at the time of filing the instant specification.

With respect to Example 5, it is the position of the examiner that a single insertion gene encoding atpG in Actinobacillus pleuropneumoniae (App.) was identified, and the example suggests (page 40, lines 1-2 "other bacterial species of homologs to previously unknown P.multocida genes that can also be mutated to produce attenuated strains of other bacterial species") the identification of other bacterial genes; a suggestion does not show possession of strains of bacteria that comprise mutated genes and evidence an attenuated phenotype.

What is now claimed is not a method of making an attenuated strain of Pasteurellacace bacteria as argued by Applicant, but actual strains of attenuated Pasteruellaceae bacteria with specific mutations in atpG genes or functional homologs thereof. In light of the evidence made of record above showing the genetic organization of genes for the Family of Pasteurellaceae being located in highly variable locations, and the operons evidencing genetic polymorphisms across the claimed Family of bacteria (see cited references above), the exemplified two species of bacteria, do not provide a representative number of species for the instantly claimed genus of

attenuated Pasteurellaceae bacteria with attenuating mutations in an atpG gene, or gene homolog thereof. The rejection is maintained for reasons of record in paper number 23.

15. The rejection of claims 7-24 and 31, as previously applied to claims 8-24 and 31-33 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reciting the phrases "a gene" ,"homolog" and activity of the homolog gene product that has not been defined, is traversed on the grounds that the specification at page 5 defines the phrase "species homologs to include genes found in two or more different species which possess substantial polynucleotide sequence homology and possess the same or similar, biological function and/or properties."

16. It is the position of the examiner that citing a definition that only functionally defines an invention that is claimed based upon structural criticality is not distinctly claimed. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. What the claimed mutant homologs are, that evidence only a relative similar function, and only share a relative substantial sequence homology does not distinctly claim Applicant's invention.

17. The rejection of claims 7-24 and 31, as previously applied to claims 8-24, 31-33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which applicant regards as the invention, for reciting mutations in homolog genes and gene products not clearly set forth in the claims, is traversed on the grounds that "The Applicants submit that they do not need to specifically point out where the mutation is located in the sequence. Indeed, in claims to transgenic animal comprising a "knockout" of a particular endogenous gene, the claims are not limited to the specific disruption or SEQ ID NO . disclosed, see e.g. 5,714,667; 5,777,195; 6087,555; and 6,100,445."

18. The examiner upon consideration of the rejection made of record, maintained the rejection because the mutation in the homolog gene and homolog gene product, which results in a specific functional characteristic of decreased expression were not clearly set forth in the claims. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

Upon consideration of Applicant's assertion that there is not requirement for the claims to recite a specific SEQ ID NO or to "specifically point out where the mutation is located in the sequence" relative to the cited patents (US Pat. 5,714,667; 5,777,195; 6087,555; and 6,100,445) and claims drawn to "knockout" transgenic animals of a particular endogenous gene, it is the position of the Examiner that:

a. US Pat. 5,714,667 claims a specific species of invention, a knockout mouse gene designated CTLA-4 (claim 1), the sequence of which is known in 1987 (see Brunet et al, Nature, Vol. 328, pages 267), col. 1, lines 14-16.

b. US Pat. 5,777,195 claims a specific species of invention, a knockout mouse gene designated DARPP-32 (claim 1, col. 15, lines 59-64), the wild type gene of which is shown in Figure 1A and described by reference 1, Walaas et al, Nature, Vol. 301, pages 69-71 (col. 15, lines 23-24 and col. 1, lines 49-52) and shows in Figures 1B and C, how the specific species of invention was produced.

c. US Pat. 6087555 and claims a species of invention directed to a knockout mouse lacking a functional endogenous OPG gene and discloses the nucleic acid for mouse OPG (see col. 1, lines 9-13; col. 1, lines 22-54) as being known.

d. US Pat. 6100445 claims a species of invention directed to a knockout mouse lacking a functional ICE gene, the sequence of the coding sequence being known (see col. 7, lines 23-29).

Therefore, all of the cited Patents provide evidence that the instantly claimed genus of inventions are the same type of inventions claimed in the cited patents which are directed specific species of gene, the sequences of which were known in the art.

What is now claimed is a genus of bacterial mutant atpG genes from strains and species of bacteria in the Family of Pasteurellaceae, the sequences of which are not own in the art and mutant attenuated strains that comprise mutant species homolog genes, the sequences of which are not known in the art. The rejection under 35 USC 112, second paragraph is maintained for reasons of record in paper number 23.

Applicant states "The rejection does not put forth any reasoning as to why, for purposes of definiteness, a claim directed to a bacteria lacking expression of a particular gene must

distinctly claim the mutation, whereas a claim directed to an animal lacking expression of a particular gene does not.

It is the position of the examiner that the genus of claimed attenuated bacteria directed to mutant species homolog genes, are not particular genes, as they must only evidence a similar function to atpG, and this function is no so claimed to be any particular similar function, and is not limited to any specific gene in any particular genus and species or strain of bacteria, while the allowed claims in the US Pat. 5,714,667; 5,777,195; 6087,555; and 6,100,445 are directed to a single gene found in a mouse, not a genus of genes from any mammal, with a similar function (homologs). What is now claimed are attenuated strains with mutations in any atgG genes or similar functional homologs in any member of the bacterial Family of Pasteurellaceae which is includes 100s of species and strains, not just a single species of gene from a single species of bacterial. The rejection with respect to clarity of the claimed invention does not have anything to do with bacterial genes having to be claimed based on a sequence and mouse genes do not. The mouse gene sequences were known in the art, while the bacterial gene(s) recited in the instantly claimed invention directed to atpG, are not coding sequences disclosed in the public domain as of the filing date of the instant Specification. Applicant's arguments are not commensurate in scope with the instantly claimed invention.

Claim Rejections - 35 USC § 102

1. Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Gwinn et al (Journal of Bacteriology, December 1997).

Gwinn et al disclose the instantly claimed invention directed to isolated mutant strains (see Table 1, strain IDA30; MGH101; IDR30, MGH11, 30, 31, 40, 51 and 61) of Haemophilus influenzae (a member of the Family Pasteruellaceae), the mutant strains comprising a mutation in an atpG species homolog, specifically atpA or atpB gene (see title and Table 1), wherein the strain was attenuated through reduced expression of induced competence genes (see page 7315, col. 2, second full paragraph; page 7317, col. 1, third paragraph; growth rate of MGH30 was 75% that of the wild type level (slower growth attenuation, page 7317, col. 2, paragraph 5 and page 7318, col. 1, paragraph 1; page 7318, col. 2, paragraph 4; page 7319, col. 1, paragraph 1 and col. 2, entire column narrative.)

Gwinn et al anticipates the instantly claimed mutant attenuated strains with mutations in a species homolog of atpG, specifically atpA or B, the mutant attenuated strain being a member of the Family of bacteria of Pasteurellaceae, specifically Haemophilus influenza.

Conclusion

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on 7:30-5:00 M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp

March 29, 2004

L. F. Smith

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